

WHAT IS CLAIMED IS:

1. A computer system comprising:
 - (a) a memory having stored therein data indicative of atomic co-ordinates derived from an electron density map having a resolution of at least about 4.5 Å and defining a ribofunctional locus of a large subunit of a ribosome; and
 - (b) a processor in electrical communication with the memory, the processor comprising a program for generating a three-dimensional model representative of the ribofunctional locus.
2. The computer system of claim 1, further comprising a device for providing a visual representation of the model.
3. The computer system of claim 1, wherein the atomic co-ordinates comprise at least a portion of the atomic co-ordinates deposited at the Protein Data Bank under accession number PDB ID: 1FFK, 1FFZ, 1FG0, IJJ2, 1K73, 1KC8, 1K8A, 1KD1, or 1K9M.
4. The computer system of claim 1, wherein the atomic co-ordinates further define at least a portion of a protein synthesis inhibitor in association with a ribofunctional locus.
5. The computer system of claim 6, wherein the protein synthesis inhibitor is an antibiotic.
6. The computer system of claim 5, wherein the protein synthesis inhibitor is anisomycin, blasticidin, carbomycin A, sparsomycin, spiramycin, tylosin, virginiamycin M, azithromycin, linezolid, or erythromycin.
7. The computer system of claim 5, wherein the atomic co-ordinates comprise at least a portion of the atomic co-ordinates recorded on Disk No. 1 under file name anisomycin.pdb, blasticidin.pdb, carbomycin.pdb, sparsomycin.pdb, spiramycin.pdb, tylosin.pdb, virginiamycin.pdb, ANISOMYC.PDB, BLASTICI.PDB, CARBOMYC.PDB, SPARSOMY.PDB, SPIRAMYC.PDB, TYLOSIN.PDB, VIRGINIA.PDB, AZITHROM.PDB, LINEZOLI.PDB, azithromycin.pdb, linezolid.pdb, or erythromycin.pdb.

8. The computer system of claim 1, wherein the ribofunctional locus comprises at least a portion of an active site in the ribosomal subunit.
9. The computer system of claim 8, wherein the active site comprises at least a portion of a peptidyl transferase site.
10. The computer system of claim 9, wherein the peptidyl transferase site is defined by a plurality of residues set forth in Table 5A or Table 5B.
11. The computer system of claim 1, wherein the ribofunctional locus comprises at least a portion of an A-site.
12. The computer system of claim 11, wherein the A-site is defined by a plurality of residues set forth in Table 6A or Table 6B.
13. The computer system of claim 1 or 11, wherein the ribofunctional locus comprises at least a portion of a P-site.
14. The computer system of claim 13, wherein the P-site is defined by a plurality of residues set forth in Table 7A or Table 7B.
15. The computer system of claim 1 or 11, wherein the ribofunctional locus comprises at least a portion of a polypeptide exit tunnel.
16. The computer system of claim 15, wherein the exit tunnel is defined by a plurality of residues set forth in Table 8A, Table 8B, Table 9 or Table 10.
17. The computer system of claim 13, wherein the ribofunctional locus comprises at least a portion of a polypeptide exit tunnel.
18. The computer system of claim 17, where the exit tunnel is defined by a plurality of residues set forth in Table 8A, Table 8B, Table 9 or Table 10.
19. The computer system of claim 1, wherein the ribofunctional locus is defined by a plurality of residues set forth in Table 11A, Table 11B, Table 12A, Table 12B, Table 13A, Table 13B, Table 14A, Table 14B, Table 15A, Table 15B, Table 16A, Table 16B,

Table 17A, Table 17B, Table 18A, Table 18B, Table 19A, Table 19B, Table 20A or Table 20B.

20. The computer system of claim 1, wherein the atomic co-ordinates are produced by molecular modeling.
21. The computer system of claim 1 or 20, wherein the atomic co-ordinates are produced by homology modeling using at least a portion of the atomic co-ordinates deposited at the Protein Data Bank under accession number PDB ID: 1FFK, 1FFZ, 1FG0, 1JJ2, 1K73, 1KC8, 1K8A, 1KD1, or 1K9M.
22. The computer system of claim 1 or 20, wherein the atomic co-ordinates are produced by molecular replacement using at least a portion of the atomic co-ordinates deposited at the Protein Data Bank under accession number PDB ID: 1FFK, 1FFZ, 1FG0, 1JJ2, 1K73, 1KC8, 1K8A, 1KD1, or 1K9M.
23. The computer system of claim 1, wherein the ribofunctional locus is defined by atoms of a ribosomal RNA.
24. The computer system of claim 1 or 23, wherein the ribofunctional locus is defined by atoms of a ribosomal protein.
25. The computer system of claim 1, wherein the atomic co-ordinates define a residue that is present in a ribosome of a pathogen but absent from a ribosome of a host organism.
26. The computer system of claim 25, wherein the host organism is a mammal.
27. The computer system of claim 26, wherein the mammal is a human.
28. The computer system of claim 1, wherein the atomic co-ordinates define residues that are conserved among one or more pathogens or disease states.
29. The computer system of method of claim 1, wherein the atomic co-ordinates define a residue present in a prokaryotic ribosome but absent from a eukaryotic ribosome or a eukaryotic mitochondrial ribosome.

30. The computer system of claim 29, wherein the eukaryotic ribosome is a mammalian ribosome.
31. The computer system of claim 1, further comprising a program for performing drug design.
32. A molecular model produced by the computer system of claim 1.
33. A method of identifying a candidate molecule, the method comprising the steps of:
 - (a) providing a molecular model of a ribofunctional locus of a large subunit of a ribosome, wherein the molecular model is defined by atoms derived from an electron density map having a resolution of at least about 4.5 Å; and
 - (b) using the model to identify a candidate molecule having a surface complementary to the ribofunctional locus.
34. The method of claim 33, wherein the candidate molecule binds the ribofunctional locus of the large subunit of the ribosome.
35. The method of claim 33, comprising the additional step of producing the candidate molecule identified in step (b).
36. The method of claim 33 or 35, comprising the additional step of determining whether the candidate molecule modulates ribosomal activity.
37. The method of claim 36, comprising the additional step of identifying a modified molecule.
38. The method of claim 37, comprising the additional step of producing the modified molecule.
39. The method of claim 38, comprising the additional step of determining whether the modified molecule modulates ribosomal activity.
40. The method of claim 39, comprising the additional step of producing the modified molecule.

41. The method of claim 33, wherein the candidate molecule is an antibiotic or an antibiotic analogue.
42. The method of claim 37, wherein the modified molecule is an antibiotic or an antibiotic analogue.
43. The method of claim 41, wherein the antibiotic or antibiotic analogue is a macrolide.
44. The method of claim 33, wherein the ribofunctional locus comprises at least a portion of an active site.
45. The method of claim 44, wherein the active site comprises at least a portion of a peptidyl transferase site.
46. The method of claim 44, wherein the peptidyl transferase site is defined by a plurality of residues set forth in Table 5A or Table 5B.
47. The method of claim 33, wherein the ribofunctional locus comprises at least a portion of an A-site.
48. The method of claim 47, wherein the A-site is defined by a plurality of residues set forth in Table 6A or Table 6B.
49. The method of claim 33 or 47, wherein the ribofunctional locus comprises at least a portion of a P-site.
50. The method of claim 49, wherein the P-site is defined by a plurality of residues set forth in Table 7A or Table 7B.
51. The method of claim 33 or 47, wherein the ribofunctional locus comprises at least a portion of a polypeptide exit tunnel.
52. The method of claim 51, wherein the exit tunnel is defined by a plurality of residues set forth in Table 8A, Table 8B, Table 9, or Table 10.
53. The method of claim 49, wherein the ribofunctional locus comprises at least a portion of a polypeptide exit tunnel.

54. The method of claim 53, wherein the exit tunnel is defined by a plurality of residues set forth in Table 8A, Table 8B, Table 9, or Table 10.
55. The method of claim 33, wherein the ribofunctional locus is defined by a plurality of residues set forth in Table 11A, Table 11B, Table 12A, Table 12B, Table 13A, Table 13B, Table 14A, Table 14B, Table 15A, Table 15B, Table 16A, Table 16B, Table 17A, Table 17B, Table 18A, Table 18B, Table 19A, Table 19B, Table 20A, or Table 20B.
56. The method of claim 33, wherein the molecular model is in an electronic form.
57. The method of claim 33, wherein the molecular model is generated from atomic coordinates produced by molecular modeling.
58. The method of claim 33 or 57, wherein the molecular model is generated from atomic coordinates produced by homology modeling using at least a portion of the atomic coordinates deposited at the Protein Data Bank under accession number PDB ID: 1FFK, 1FFZ, 1FG0, 1JJ2, 1K73, 1KC8, 1K8A, 1KD1, or 1K9M.
59. The method of claim 33 or 57, wherein the molecular model is generated from atomic coordinates produced by molecular replacement using at least a portion of the atomic coordinates deposited at the Protein Data Bank under accession number PDB ID: 1FFK, 1FFZ, 1FG0, 1JJ2, 1K73, 1KC8, 1K8A, 1KD1, or 1K9M.
60. The method of claim 33, wherein the molecular model comprises residues that are conserved among one or more prokaryotic organisms.
61. The method of claim 33, wherein the molecular model comprises a residue that is present in a prokaryotic ribosome but is absent from a eukaryotic ribosome or a eukaryotic mitochondrial ribosome.
62. The method of claim 61, wherein the eukaryotic ribosome is a mammalian ribosome.
63. A computer system comprising:
 - (a) a memory having stored therein data indicative of atomic co-ordinates derived from an electron density map defining at least a portion of a protein synthesis inhibitor

when the protein synthesis inhibitor is interacting with a ribofunctional locus of a large subunit of a ribosome; and

(b) a processor in electrical communication with the memory, the processor comprising a program for generating a three-dimensional model representative of at least a portion of the protein synthesis inhibitor.

64. The computer system of claim 63, further comprising a device for providing a visual representation of the model.
65. The computer system of claim 63, wherein the protein synthesis inhibitor is an antibiotic.
66. The computer system of claim 65, wherein the protein synthesis inhibitor is anisomycin, blasticidin, carbomycin A, sparsomycin, spiramycin, tylosin, virginiamycin M, azithromycin, linezolid, or erythromycin.
67. The computer system of claim 66, wherein the atomic co-ordinates comprise at least a portion of the atomic co-ordinates recorded on Disk No. 1 under file name: anisomycin.pdb, blasticidin.pdb, carbomycin.pdb, sparsomycin.pdb, spiramycin.pdb, tylosin.pdb, virginiamycin.pdb, ANISOMYC.PDB, BLASTICI.PDB, CARBOMYC.PDB, SPARSOMY.PDB, SPIRAMYC.PDB, TYLOSIN.PDB, VIRGINIA.PDB, AZITHROM.PDB, LINEZOLI.PDB, azithromycin.pdb, linezolid.pdb, or erythromycin.pdb.
68. The computer system of claim 63, wherein the ribofunctional locus comprises at least a portion of an active site.
69. The computer system of claim 68, wherein the active site comprises at least a portion of a peptidyl transferase site.
70. The computer system of claim 68, wherein the ribofunctional locus comprises at least a portion of an A-site.
71. The computer system of claim 68 or 70, wherein the ribofunctional locus comprises at least a portion of a P-site.

72. The computer system of claim 68 or 70, wherein the ribofunctional locus comprises at least a portion of a polypeptide exit tunnel.
73. The computer system of claim 71, wherein the ribofunctional locus comprises at least a portion of a polypeptide exit tunnel.
74. A method of identifying a lead candidate, the method comprising the steps of:
 - (a) providing a molecular model of at least a portion of a protein synthesis inhibitor when the protein synthesis inhibitor is interacting with a ribofunctional locus of a large subunit of a ribosome; and
 - (b) using the model to identify the lead candidate.
75. The method of claim 74, wherein the lead candidate is capable of interacting with the ribofunctional locus.
76. The method of claim 74, wherein the lead candidate is capable of binding the ribofunctional locus.
77. The method of claim 74, comprising the additional step of producing the lead candidate identified in step (b).
78. The method of claim 74 or 77, comprising the additional step of determining whether the lead candidate modulates ribosomal activity.
79. The method of claim 78, comprising the additional step of modifying the lead candidate.
80. The method of claim 79, comprising the additional step of producing the modified lead candidate.
81. The method of claim 80, comprising the additional step of determining whether the modified lead candidate modulates ribosomal activity.
82. The method of claim 81, comprising the additional step of producing the modified lead candidate.

83. The method of claim 74, wherein the lead candidate is an antibiotic or an antibiotic analogue.
84. The method of claim 74, wherein the lead candidate is a hybrid antibiotic.
85. The method of claim 84, wherein the lead candidate comprises at least a portion of a first antibiotic and at least a portion of a second, different antibiotic.
86. The method of claim 82, wherein the modified lead candidate is an antibiotic or an antibiotic analogue.
87. The method of claim 86, wherein the antibiotic or antibiotic analogue is a macrolide.
88. The method of claim 74, wherein the protein synthesis inhibitor is an antibiotic.
89. The method of claim 88, wherein the antibiotic is anisomycin, blasticidin, carbomycin A, sparsomycin, spiramycin, tylosin, virginiamycin M, azithromycin, linezolid, or erythromycin.
90. The method of claim 89, wherein the molecular model is defined by at least a portion of the atomic co-ordinates recorded on Disk No. 1 under file name: anisomycin.pdb, blasticidin.pdb, carbomycin.pdb, sparsomycin.pdb, spiramycin.pdb, tylosin.pdb, virginiamycin.pdb, ANISOMYC.PDB, BLASTICI.PDB, CARBOMYC.PDB, SPARSOMY.PDB, SPIRAMYC.PDB, TYLOSIN.PDB, VIRGINIA.PDB, AZITHROM.PDB, LINEZOLI.PDB, azithromycin.pdb, linezolid.pdb, or erythromycin.pdb.
91. The method of claim 74, wherein the ribofunctional locus comprises at least a portion of an active site.
92. The method of claim 91, wherein the active site comprises at least a portion of a peptidyl transferase site.
93. The method of claim 91, wherein the ribofunctional locus comprises at least a portion of an A-site.

94. The method of claim 74 or 93, wherein the ribofunctional locus comprises a least a portion of a P-site.
95. The method of claim 74 or 93, wherein the ribofunctional locus comprises at least a portion of a polypeptide exit tunnel.
96. The method of claim 94, wherein the ribofunctional locus comprises at least a portion of a polypeptide exit tunnel.
97. The method of claim 74, wherein the molecular model is in an electronic form.
98. The method of claim 74, wherein the molecular model is generated from atomic coordinates produced by molecular modeling.
99. A protein synthesis inhibitor comprising:
 - a first binding domain having a surface that mimics or duplicates a surface of a known first molecule that binds with a first contact site in a large ribosomal subunit; and
 - a second binding domain having a surface that mimics or duplicates a surface of a known second molecule that binds with a second contact site in the ribosomal subunit,

wherein the first domain is attached to the second domain so as to permit both the first domain and the second domain to bind with its respective contact site thereby to disrupt protein synthesis in a ribosomal subunit, and wherein the protein synthesis inhibitor has a molecular weight of less than about 1,500 and an IC₅₀ lower than about 50 μM.
100. The inhibitor of claim 99, wherein the first molecule is a first antibiotic.
101. The inhibitor of claim 100, wherein the first antibiotic binds at least a portion of a ribofunctional locus.
102. The inhibitor of claim 99 or 100, wherein the second molecule is a second antibiotic.
103. The inhibitor of claim 102, wherein the second antibiotic binds at least a portion of a ribofunctional locus.

104. An engineered, synthetic protein synthesis inhibitor comprising:

a binding domain having a surface that mimics or duplicates a surface of a known molecule which binds with a contact site in a ribosomal subunit; and

an effector domain attached to the binding domain which, upon binding of the binding domain with the contact site, occupies a space within or adjacent the ribosomal subunit thereby to disrupt protein synthesis in the ribosomal subunit, wherein the protein synthesis inhibitor has a molecular weight less than 1,500 and has an IC₅₀ lower than about 50 μM.

105. The inhibitor of claim 104, wherein the surface of the binding domain mimics or duplicates a surface of a known antibiotic which binds with the contact site.

106. A protein synthesis inhibitor comprising:

a molecule capable of contacting at least three residues but less than thirteen residues in Table 11A that together define an anisomycin binding pocket of a large ribosomal subunit;

a molecule capable of contacting at least three residues but less than twenty residues in Table 12A that together define a blasticidin binding pocket of a large ribosomal subunit;

a molecule capable of contacting at least three residues but less than sixteen residues in Table 13A that together define a carbomycin A binding pocket of a large ribosomal subunit;

a molecule capable of contacting at least three residues but less than twenty residues in Table 14A that together define a tylosin binding pocket of a large ribosomal subunit;

a molecule capable of contacting at least three residues but less than nine residues in Table 15A that together define a sparsomycin binding pocket of a large ribosomal subunit;

a molecule capable of contacting at least three residues but less than thirteen residues in Table 16A that together define a virginiamycin M binding pocket of a large ribosomal subunit;

a molecule capable of contacting at least three residues but less than fifteen residues in Table 17A that together define a spiramycin binding pocket of a large ribosomal subunit;

a molecule capable of contacting at least three residues but less than thirteen residues in Table 18A that together define an erythromycin binding pocket of a large ribosomal subunit;

a molecule capable of contacting at least three residues but less than eleven residues in Table 19A that together define an azithromycin binding pocket of a large ribosomal subunit; or

a molecule capable of contacting at least three residues but less than fifteen residues in Table 20A that together define a linezolid binding pocket of a large ribosomal subunit.